Application Process for Testing Specific Agents through the Pediatric Preclinical Testing Program

Initial presentation of an agent to the Pediatric Drug Development Group (PedDDG) should be made through the Project Officer. The Project Officer coordinates with the agent sponsor the preparation of an application that will address the topics listed below, as they are relevant to the proposed agent. If the agent sponsor already has a prepared document (e.g., an Investigator's Brochure) that contains the information requested below, this may be submitted along with a cover letter addressing those topics that are not adequately addressed in the prepared document. The agent application including appendix is due at least two weeks prior to the PedDDG meeting. Applications (excluding appendices) should not exceed 10 pages in length.

- *Background Information*: sufficient information to identify and clarify the scientific and medical context from which the opportunity emerges.
- *Preclinical molecular target studies*: Sufficient information should be provided to document the degree of specificity of the agent for its claimed molecular target(s).
- *Preclinical In Vitro Studies*: Data from both single agent *in vitro* studies and combination *in vitro* studies, if performed, should be provided.
- *Preclinical In Vivo Studies*: Available data concerning the *in vivo* anticancer activity of the agent should be provided. In general, appropriate agent administration schedules for demonstrating anti-cancer activity and the maximum tolerated doses for these schedules should be known at the time that an agent is proposed for PPTP testing. For most agents, these data will likely be primarily taken from adult cancer preclinical models, but data from pediatric models should be provided as well when available. Data from both single agent *in vivo* studies and combination *in vivo* studies, if performed, should be provided.
- *Preclinical Pharmacokinetics*: Of particular interest is the availability of pharmacokinetic data from preclinical models used to demonstrate efficacy.
- *Commitment to Clinical Development*: Priority is given to studying agents that are entering adult clinical evaluation and that may have potential applicability in the childhood cancer setting. Information concerning the current status of clinical development of the agent should be provided, along with any plans for potential pediatric evaluations of the agent.
- *Additional Support*: Any support that the agent sponsor can provide towards the PPTP evaluation of the agent should be described, including performance of laboratory testing for pharmacokinetic or pharmacodynamic studies (e.g., testing to document modulation of the agent's target in tumor tissue).
- *Intellectual Property*: information regarding any patents issued or pending with respect to the product. In addition, the application should indicate the willingness of the sponsor to negotiate Material Transfer Agreements (MTAs) with NCI based on the model MTAs that have been developed by NCI for the PPTP. These MTAs were developed by NCI in collaboration with pharmaceutical sponsors and academic research centers. The provisions included in the model MTAs have been accepted by all of the PPTP institutions.
- *Quantity of Agent Available*: The quantity of agent available for testing should be provided. For reference, the PPTP *in vivo* testing program contains 47 xenograft lines, and Stage I testing at the MTD for two courses across the entire panel requires approximately 28.2-37.6 mg of agent for every 1 mg/kg of agent administered per course.
- *Appendix*: background preprints or reprints.

The PedDDG Meeting for Agent Review

At the time of the PedDDG Meeting, the Project Officer will present a summary of the agent. In selected cases, the agent sponsor may participate in the meeting (either in person or by tele/video-conference) and may present the agent and address questions about the agent. In

this situation, the sponsor will leave the meeting after the presentation and the question and answer period.

Approval of new agents for testing through the PPTP will be based on a number of factors, which are briefly described below.

- The agent should generally be one for which clinical testing in children is considered a potential priority, with testing able to begin within 12-24 months. Satisfactorily addressing this criterion will generally imply an active development plan for the agent for adult cancers and a willingness to consider pediatric evaluations of the agent.
- The agent should have plausible relevance to the treatment of childhood cancers, based on current understanding of the mechanism of action of the agent and current understanding of the biology of childhood cancers. Agents that affect molecular targets that have been prioritized by the PedDDG are presumed to meet this criterion.
- Agents with molecular targets or mechanisms of action that have not been previously addressed by the PPTP will be prioritized higher than agents whose molecular targets have previously been addressed by the PPTP.
- Most agents selected for testing will have undergone extensive prior testing against adult preclinical cancer models. For these agents, information concerning drug formulation and optimal schedule/dosing needs to be available to PPTP investigators so that a testing plan for the agent can be developed.
- Quantity of agent available for testing. The availability of sufficient quantity of agent for testing against the entire PPTP panel will favor one agent over a similar agent addressing the same target for which less agent is available for testing.

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